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# Newfangled Quantitative Pharmacia (Isradipine) Stratagem: Quality by Design (Qbd) Taguchi Array via Response Surface (L25 Via CCD20) Methodology

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## Abstract

Statistically ($L_{25}$ via $CCD_{20}$), a novel array via response surface analytical process was an attempt to develop a quantification of the pharmacies/bulk, Isradipine using organic medium (methanol & chloroform) as solvent. During analysis, the maximum absorption wavelength of model drug was found at lambda max 327nm and also done its recovery via validation further. In the beginning, by using a quality improvement statistically array looms (Taguchi) was generated numerous level/space (s) of the independent variable (A=methanol; B=chloroform & C=ratio of A: B) by performing experimentally ($L_{25}$ array runs to studied their response to be found the finer spaces). Additionally, a three-dimensional response surfaces strategy [RSM; three dimensional central composite designs ($CCD_{20}$)] explored variables non-factorial levels which are used as fine. Also, responses quadratic (02nd order) equation of response (Y=absorption) was predicted analytically for "finer to finest" (2.5 to 15µg/ml) by analysis alone variable space as well as together. Thus, newfangled Beer's finest in-terms of linearity, precision, sensitivity and accuracy during analysis range was found and also validated for further, finest determination. As well, economically inexpensive quantitative can be titled as newfangled analytical estimation of Isradpine ($CCB_s$, Calcium channel blocker) in bulk/Pharmacia forms.

**Keywords:** $CCB_s$; $L_{25}$; $CCD_{20}$; $3^D$- plots; Quantitative and validation

## Introduction

Globally, all through up to date for Anti-BP therapy, most potent 1,4-dihydro-pyridine; a hetero-atom carbocyclic derivative is Isradipine [1,2]. Biologically, the selected model drug pine mechanism is bound L-type of Calcium Channel blocker ($CCB_s$) flux of cardiac and also smooth muscles with prominent specificity via affinity and inhibiting [3-8]. Literature, for $CCB_s$ plentiful techno and estimation methods were like Titrimetric [9,10], spectroscopic [11-18], Fluorimetric [19-26], electrochemical [27-29], Chromatographic methods [30-38] already reported [39-42]. Therefore, except a few anti-BP drugs till date there is no analytical quality design (QbD) stratagem. So, there is in-need to be a quality of the analytical design program required, which can be used as advanced improved development, quality array via quadratic non-factorial response design [43,44].

This research attempt was to develop & estimate statistically spectrophotometer quality improved methodology by generated preliminary trials and theirs experimental responses were interpreted to find finer spaces significant variables. In addition, after that non factorials surface design with significant positive & negative finest space of variables were performed. Moreover, three-dimensional ($3^D$) surface response model plots were constructed to study and predicted the preeminent interactive effects of a "better to best" fitted space [45].

Our research foremost objective was to develop a newfangled sensitive finest plus validated quality by design analytical procedure using orthogonal array ($L_{25}$) with non-factorial response surface (also known central composite). Due to simplicity, selectivity and sensitivity quantification during development of novel statistical approach via preference to selected Ultra-visible Spectrophotometric method. Furthermore, it can be considered economically low as advanced as plain and stable quality by design "finer to finest" fitted as quantitative (Isradipine) in bulk as well as pharmacy quantify analytical stratagem.

## Experimental

The preferred drug (Isradipine standard) reference procured was as kindly gifted by Pharmaceuticals Ltd (India) and lambda maximum ($\lambda_{max}$; Figure 1) [24,39] was measured by double beam (Jasco, UV-630) spectrophotometer method [38] using one centi-meter quartz cells. All analytical grade solvents were and reagents were purchased from Lakshya Enterprises and Mercury Lab., New-Delhi, India.

## Preliminary array

Preliminary trials were conducted to elect the optimum factor levels and their working ranges having influence and major influence shown by ratio of organic phase. In order to find and study the interactive effect of factors in all possible combinations; Taguchi $L_{25}$; "0rthogonal array" statistical tools for quality improvement economical preliminary array ($L_{25}$) of significant independent variables; methanol (A), chloroform (B) & their combined ratio (C=A: B).

## Statistical design

Based on (Mini-Tab®, version 17.2.1; Taguchi) $L_{25}$ design quality,

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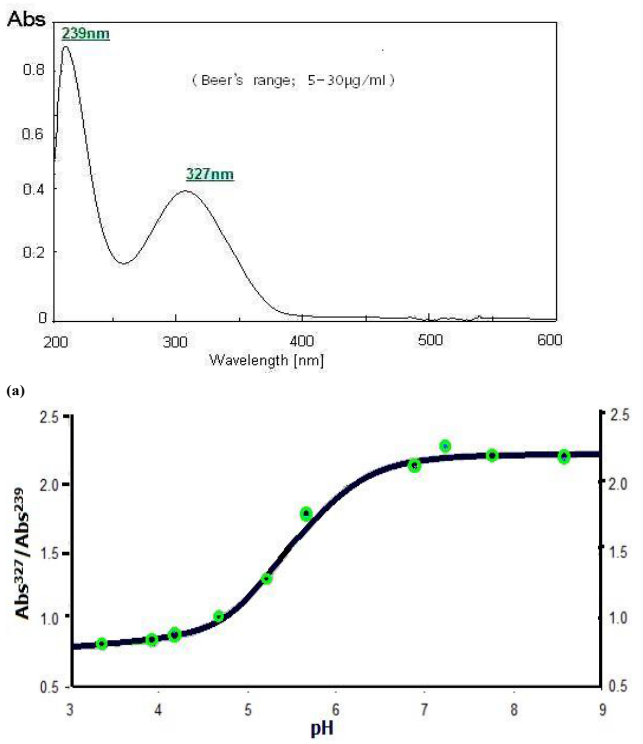



**Figure 1:** The model drug UV-visible spectra above showed; a) lambda max 327nm (consider because having low concentration 10µg/ml; b) the spectrum is recorded drug methanolic and buffer solutions at various changing the negative log of the activity of the hydrogen ion in an aqueous solution.

improve and control design was applied to experimental ranges of via factor (01, 02 & 03 integers of arrays at a time has to be altered) performed. Thus, generated twenty (Isra-1 to 25) run via five levels (Table 1) were diluted with analytical grade solvents (anhydrous methanol) for final concentration (10µg/ml). Subsequently, as per positive & negative spaces finally solutions absorbance ($\lambda_{max}$ 327nm) was measured against blank an organic experimental background. Therefore, the responses (Y) obtained for each trial's "Signal to Noise" values were calculated for the responses individual as well as simultaneously together. The resulted signal to noise ratio corresponding to responses demonstrated a variety of S/N ratio for a suitable parameter for response analysis. By using a factorial independent methodology, i.e. Central Composite Design (CCD) runs and done experimentally which is also used as another tool [45] to study the interactive effects by using three dimensional surface response methodology (RSM)

**Response $3^{-D}$ surface analysis (RSM) :** After array, a static statistical without constraining of fractional or independent or non-factorial independent methodology, design, function, program (significant variable & its finest level) was used (Table 1). The better (finer) level of each significant variables were found after a non-factorial quadratic response surface [43]; three-dimensional methodology was used for design finest (positive to negative level) spaces. By means of three dimensional plot model fitness, to find out the variable "finer to finest" fitted level & their ratios which can be statistically finest originated quality by design using Taguchi array via Surface response; $L_{25}$ via $3^{-D}$" QbD methodology [44-45]. At optimum levels the of designed plots of (absorbance=Y response) surface data ($3^{D}$) model were analysised, moreover independently factorial generated equation were included all statistically coefficients of each level response (Table 2). Moreover, the recovery as well as validation study was carried-out; using powder containing the equivalent drug weight amount was calculated recovery in percentages [46-47].

## Quality by design (QbD) Spaces analysis

Based on the prediction, at random (05; five) formulas were elected and their responses were evaluated. The validation for RSM involving all the five checkpoint formulations was found to be within limits. The quantitative responses for different combinations of independent variables were obtained experimentally and the results were found to fit the design model.

## Result and Discussion

The stash solution of model drug (05 mg) was prepared in organic medium with followed methanol to obtain concentration (50 µg/ml). The aliquots were prepared pipette out which diluted with dry methanol to made up volumetric to desired range (Beer's 5 to 30 µg/ml; Figure 1a) and furthermore, also studied numerous the negative log of the activity of the hydrogen ion (pH; pKa) in an organic solution by spectrophotometric scanned the solution (10 µg/ml) at 327nm (Figure 1b).

## Orthogonal study

The array ($L_{25}$) was helped to find out optimum "Better to Best" as finer level of significant variables which further used as quadratic as an independent design explored to develop a superior quality with economically simple program (Table 1). The signal to noise effect plot was drawn for each factor at different levels by taking levels as x-coordinates and S/N ratio as y-coordinates (Figure 2). The degree of variances posed by each factor and ANOVA results for suggested factors 'A & C (i.e. Ratio of A with respect to B has to be most significant factor affecting (73.6%) responses (Y=absorbance), whereas B (4.35%) has least significant. The results for responses were interpreted by Signal to Noise studies (S/N) ratio for best accuracy considered of measured data.

**S/N analysis:** The better fitted value of S/N ratios with an observed S/N ratio was obtained. Furthermore, the results of ANOVA were confirmed by analysis of mean S/N ratio obtained for each factor (A, B & C) at 01 to 03 levels and influences of factors were predicted considering responses of S/N ratios (Table 1). The response of mean S/N ratio also confirmed to be the most significant factor A followed by C & B better to best array codes; A3B1C3; A3B2C4; A3B5C5; A4B1C4 & A4B5C3 were highlighted; fit 99.98 to 99.99 in percentages; depicted in Table 1). However, it also indicated that these levels further can be applicable for "finer to finest" development of analytical ratio using i.e. Central Composite Design of experiment which is a tool of response surface ($3^{-D}$ model) methodology to study the interactive effects.

## CCD: $3^{D}$ RSM

In addition again, generated (FF-1 to 20; Table 2) using finer to finest (-0.5 to +0.5; negative to positive space runs) levels (significant variables) performed (experimentally vs predicted value in Table 2) and analyze their responses. The central composite surface design (RSM) generated the second-order poly-nominal equation of design models and predicted levels. Further, finer to finest level of significant variable (A and C followed by B) fitted with positive (+0.5) and negative (-0.5) space of selected finer experiment with predicted finest quadratic model values (depicted in Table 2) of response (Y). Substantial, "finer

| Factorial Array and their responses at positive & negative [(+) & (-)] spaces | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Spaces** | Levels | **A** | **Variables Unit** | **B** | **C** in terms | | Coded |
| | | | | | **Ratio** | **A: B ml** | |
| **Negative** | -1.0 | 4 | | 6 | 0.5 | 1 : 2 | **1** |
| | -0.5 | 5 | | 5 | 1.0 | 2 : 2 | **2** |
| **Zero** | Null | 6 | ml | 4 | 1.5 | 3 : 2 | **3** |
| **Positive** | +0.5 | 7 | | 3 | 2.0 | 4 : 2 | **4** |
| | +1.0 | 8 | | 2 | 2.5 | 5 : 2 | **5** |

| Designed trails three factor at five level ($3^{*5}$) array of Smaller is Better level(s) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Solutions Analysis No.** | **Factorial Levels** | | | **Response** | | **Recovery** (in terms | | | **Analytical** | **Better to Best** |
| | | | | **Absorbance** | **Mean ± SD** | **$S_iN^R$** | | **Desirability (1=100%)** | **Array** | **Finer Fitted** |
| | **A** | **B** | **C** | **Y** | **n=3** | **Actual** | **Predicted** | **Fitness** | **Codes** | **Levels** |
| Isra-01 | 1 | 1 | 1 | 0.233 | 0.263 | 12.653 | 11.698 | -0.030 | A1B1C1 | |
| Isra-02 | 1 | 2 | 2 | 0.252 | 0.268 | 11.972 | 11.520 | -0.020 | A1B2C2 | |
| Isra-03 | 1 | 3 | 3 | 0.276 | 0.283 | 11.182 | 10.987 | -0.010 | A1B3C3 | |
| **Isra-04** | 1 | 4 | 4 | 0.291 | 0.270 | 10.722 | 11.378 | **0.980** | | **A1B4C4** |
| **Isra-05** | 1 | 5 | 5 | 0.312 | 0.281 | 10.117 | 11.063 | **0.970** | | **A1B5C4** |
| Isra-06 | 2 | 1 | 2 | 0.226 | 0.229 | 12.918 | 12.799 | -0.003 | A2B1C2 | |
| Isra-07 | 2 | 2 | 3 | 0.235 | 0.241 | 12.579 | 12.372 | -0.006 | A2B2C3 | |
| **Isra-08** | 2 | 3 | 4 | 0.248 | 0.233 | 12.111 | 12.582 | **0.980** | | **A2B3C4** |
| Isra-09 | 2 | 4 | 5 | 0.247 | 0.265 | 12.146 | 11.597 | -0.018 | A2B4C5 | |
| **Isra-10** | 2 | 5 | 1 | 0.241 | 0.229 | 12.36 | 12.763 | **0.988** | | **A2B5C1** |
| **Isra-11** | 3 | 1 | 3 | 0.238 | 0.236 | 12.469 | 12.570 | **0.998** | | **A3B1C3** |
| **Isra-12** | 3 | 2 | 4 | 0.231 | 0.225 | 12.728 | 12.885 | **0.994** | | **A3B2C4** |
| Isra-13 | 3 | 3 | 5 | 0.247 | 0.261 | 12.146 | 11.719 | -0.014 | A3B3C5 | |
| Isra-14 | 3 | 4 | 1 | 0.241 | 0.246 | 12.360 | 12.214 | -0.005 | A3B4C4 | |
| **Isra-15** | 3 | 5 | 2 | 0.238 | 0.228 | 12.469 | 12.783 | **0.990** | | **A3B5C5** |
| **Isra-16** | 4 | 1 | 4 | 0.290 | 0.274 | 10.752 | 11.294 | **0.984** | | **A4B1C4** |
| Isra-17 | 4 | 2 | 5 | 0.294 | 0.307 | 10.633 | 10.233 | -0.013 | A4B2C5 | |
| Isra-18 | 4 | 3 | 1 | 0.290 | 0.296 | 10.752 | 10.548 | -0.006 | A4B3C1 | |
| Isra-19 | 4 | 4 | 2 | 0.297 | 0.300 | 10.545 | 10.446 | -0.003 | A4B4C2 | |
| **Isra-20** | 4 | 5 | 3 | 0.295 | 0.290 | 10.604 | 10.765 | **0.995** | A4B5C3 | |
| Isra-21 | 5 | 1 | 5 | 0.333 | 0.320 | 9.5511 | 9.9813 | -0.4302 | A5B1C5 | |
| **Isra-22** | 5 | 2 | 1 | 0.335 | 0.306 | 9.4991 | 10.401 | **0.971** | | **A5B2C1** |
| **Isra-23** | 5 | 3 | 2 | 0.325 | 0.314 | 9.7623 | 10.118 | **0.989** | | **A5B3C2** |
| Isra-24 | 5 | 4 | 3 | 0.330 | 0.325 | 9.6297 | 9.7672 | -0.030 | A5B4C3 | |
| Isra-25 | 5 | 5 | 4 | 0.233 | 0.263 | 12.653 | 11.698 | -0.010 | A5B5C4 | |

Aristech (*) value indicated the significant variable (optimum) finer as better-fitted level of response; A=Methanol (ml); B=Chloroform; C=Ratio of Methanol (ml): Chloroform (ml); Y=Absorbance at lambda max 327nm of drug concentration (10µg/ml)

**Table 1:** Designed $L_{25}=3^{*5}$ Taguchi Array of selected variables and levels via constant drug concentration.

to finest fitted" design model level found which was used to develop quantification of anti-hyper tensor bulk/Pharmacia (Isradipine) using optimized and was validated simple and finest economically attempt as novel designed newfangled stratagem.

**Equation investigation:** A second-order quadratic derived equation of significant variable response (Y) at an optimized level was generated and the "finest to finest" model fitted proposed equation is;

$$Y=0.30+0.006A-0.003B+0.006C-0.001AB-0.005AC+0.004BC-0.02A^2-0.006B^2+0.021C^2;$$

Where, Y =absorbance and A, B & C; amount of methanol, chloroform & ratio of organic phase in milli-liter unit. In this case, "Prob>F" less than (p>0.0500) indicated ("Model F-value" 217.10) model significant terms are A, B, AB, AC, BC, $A^2$, $B^2$, $C^2$ along with positive or negative spaces had a more pronounced effect. However, probability values greater (p<0.1) indicated that the model terms are not significant implies the model is significant. There is only a 0.01% chance that a designed model $F_{Value}$; this large could occur due to noise. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model. There is only a 0.01% chance that a "Model F-Value" (Table 2) and "Lack of Fit" of the F-value (0.90) implies, is not significant relative to the pure error and non-significant lack of fit is good.

**Model ($3^{-D}$) study:** The fitted model three dimensional model plots (Figure 3 I-IV) have been demonstrated the significant variables at independently optimized level interaction effects individually or along together at the same time on the response (Y). During model analysis, optimized "finer to finest" levels of variability (A, B & C) were negative (-0.5=6ml=A and ratio 2: 2=A: B=C=1) to positive (+0.5=7ml and ratio 4: 2=A: B=C=2) space as compared. Also, enhanced quality as finest correlation (Figure 3II) coefficient shown with response (0.277 to 0.318=Y=absorbance at finer to finest level). Therefore, this model design

| **Independent** | **Actual (Coded) levels** | | | |
|---|---|---|---|---|
| **Variables** (ml) | Negative (-0.5) | Zero (0) | Positive (+0.5) | Finer to Finest Coded |
| Methanol (right sided | 6.0 | 6.5 | 7.0 | **A** |
| Chloroform (left-sided) | 4.0 | 3.5 | 3.0 | **B** |
| Ratio A: B (Two-sided) | 1.0 | 1.5 | 2.0 | **C** |
| **Dependant** | **Constraints** | | | |
| $Y_1$ = Absorbance | $0.277 \leq Y_1 \geq 0.318$ | | | |

| **Central Composite; independent Design** | | | | | |
|---|---|---|---|---|---|
| **Runs-Code** | **Variables** | | | | |
| | **Independent** | | | **Response (Y)** | |
| | A | B | C | Observed | Predicted |
| | 0 | 0 | +0.5 | 0.318 | 0.288 |
| | +0.5 | +0.5 | +0.5 | 0.298 | 0.312 |
| | +0.5 | -0.5 | -0.5 | 0.312 | 0.277 |
| | +0.5 | -0.5 | +0.5 | 0.297 | 0.298 |
| | +0.5 | +0.5 | +0.5 | 0.296 | 0.291 |
| | 0 | 0 | -0.5 | 0.316 | 0.296 |
| | 0 | 0 | 0 | 0.295 | 0.295 |
| | 0 | 0 | 0 | 0.291 | 0.297 |
| | -0.5 | +0.5 | -0.5 | 0.277 | 0.296 |
| | +0.5 | 0 | 0 | 0.285 | 0.285 |
| | 0 | +0.5 | 0 | 0.287 | 0.290 |
| | -0.5 | -0.5 | +0.5 | 0.291 | 0.286 |
| | 0 | 0 | 0 | 0.297 | 0.316 |
| | -0.5 | +0.5 | +0.5 | 0.296 | 0.318 |
| | -0.5 | -0.5 | -0.5 | 0.289 | 0.295 |
| | 0 | 0 | 0 | 0.298 | 0.295 |
| | 0 | 0 | 0 | 0.291 | 0.294 |
| | 0 | 0 | 0 | 0.295 | 0.294 |
| | 0 | 0 | 0 | 0.296 | 0.295 |
| | 0 | -0.5 | 0 | 0.296 | 0.295 |

| "Finer to Finest" designed model equation | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Term** | **Model** | **A** | **B** | **C** | **AB** | **AC** | **BC** | **$A^2$** | **$B^2$** | **$C^2$** | **Lack of Fit** |
| $F^{value}$ | 217.1 | 350.0 | 85.9 | 3.94 | 8.76 | 197.7 | 123.2 | 554.5 | 92.4 | 1141.2 | 0.90 |
| **Significant** | | | | | **to** | | | | **Non-significant** | | |
| $p^{value;\ Prob.>F}$ | | <0.0001 | | 0.075 | 0.014 | < 0.0001 | | | | | 0.5204 |
| $R^2$ | | R-Square | | Adjusted | | Predicted | | SD | Mean | | %CV |
| **Values** | | 0.9949 | | 0.9903 | | 0.9573 | | 0.0095 | 0.30 | | 0.32 |

"Prob > F" values less than 0.0500 indicate model terms are significant and greater than 0.1000 indicate the model terms are not significant.

**Table 2:** Results of central composite designed (CCD) "finer to finest" spaces.

space can be used to investigate its surface ($3^{-D}$ plots; Figure 3I-III) which showed the independent effect of optimized as finest levels of significant variables (experimental vs predicted; Figure 3IV). The "Pred R-Squared" is in reasonable agreement with the adjusted R-squared (Table 2) and measured a desirable signal to noise ratio. As well, adequate precision (approximate 60%) value of less than 0.001 indicated that model terms are significant. Furthermore, this model designs of finer to finest" significant variables (A & C via B) levels independent effect can be used for quantitative finest levels of estimation method.

## QbD strategy

During Quality by design, quantitative methodology, the model drug (API) lambda maxima wavelength was recorded using Ultra-Violet (Jasco, Model-630) spectrophotometer at significant hydrogen-ion concentrations (pH 3.5) via finest spaces (FST-C A=methanol=6.5ml followed by chloroform=B=3.5ml and ratio 1.5=A: B=3: 2=C) of anhydrous (methanol: chloroform) solvent as blank to measured the absorbance at lambda max (λ max) 327nm relative standard deviation analysis to be with-in acceptable limit or not. The finest fitted finest model of significant variables "Finest" analytical stratagem level ratio; solutions into a flask having a drug solution were taken and finally made the volume with methanolic buffer (Isradipine; 10µg/ml; pH 3.5;) solution. The linear correlation plots drawn between the predicted and experimental values demonstrated high desirability values for absorbance as response values was observed (Table 4). The calibration curve was constructed by a plot between absorbance vs concentration (µg/ml) and showed finest beer(s) (2.5 to 15µg/ml & Y=0.29+0.005) range with well, linearity and correlation coefficient (R-square 0.9999) which indicated the excellent goodness of fit (p>0.01) at 327nm.

## Conclusion

The newfangled methodology results validation by using experimental values of the responses were compared with the

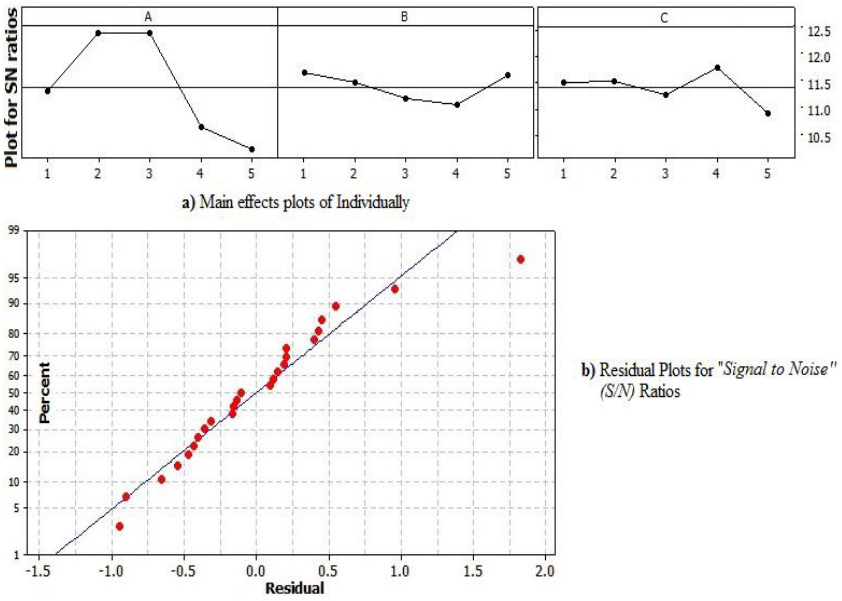



**Figure 2:** "Smaller is better" significant variables level/spaces **a)** main effect; **b)** normal probability residual plots for "Signal to Noise" (S/N).

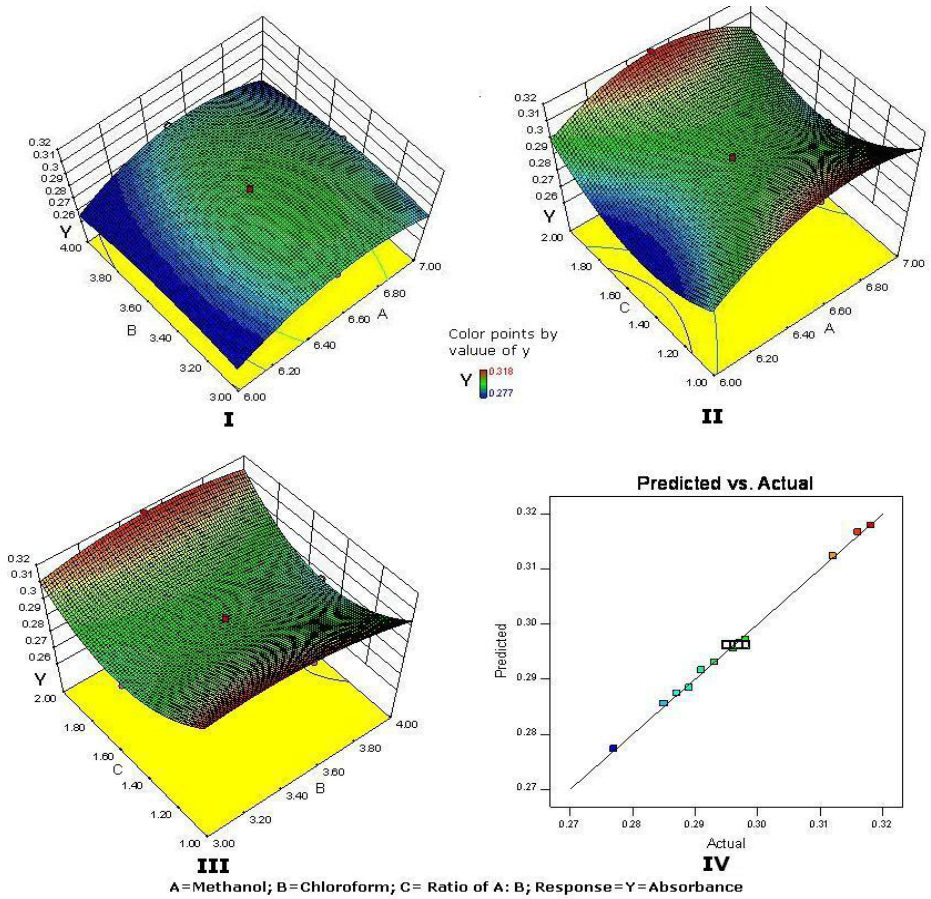
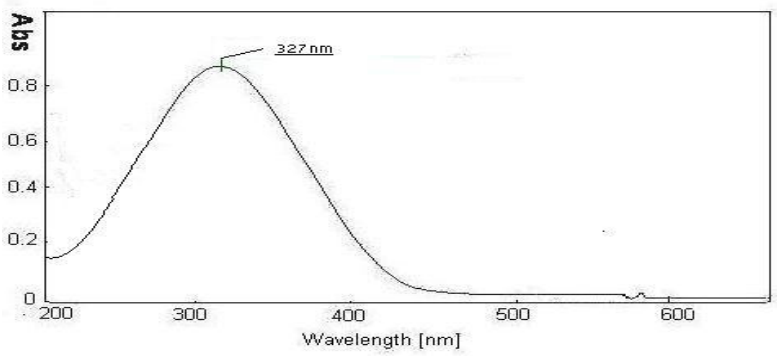
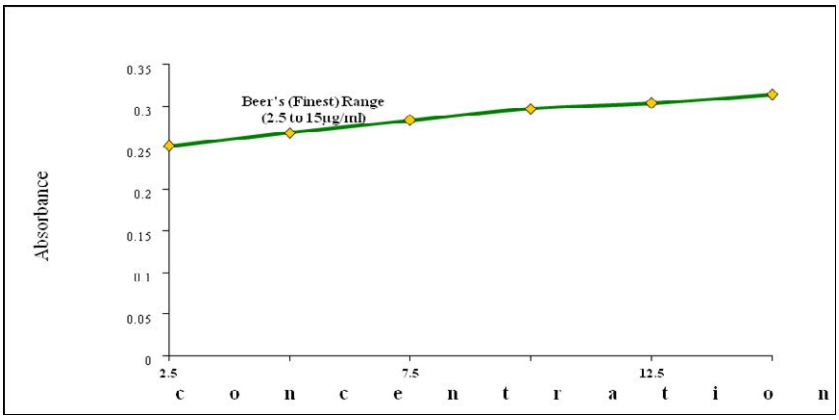



**Figure 3:**Three dimensional ($3^{-D}$; response surface) plots shown interactive effect of I) A & B II) A & C; III) B & C at a time two variables respectively; IV) a linear correlation actual *vs* predicted values of response (Y=absorbance).




a)




b)

**Figure 4:** UV-spectrum of model drug: a) lambda max finest significant variables level; b) a linear correlation of newfangled range.

| Finest | Methanol (A) | Chloroform (B) | Ratio (A: B) | Absorbance ($Y_{FST}$) | Fitness | |
|---|---|---|---|---|---|---|
| | | | | | Desirability (1) | Error |
| FST-A | 6.10 | 3.00 | 1.00 | 0.2969 | 0.960 | 0.040 |
| FST-B | 6.25 | 3.75 | 1.70 | 0.2910 | 0.860 | 0.150 |
| **FST-C** | 6.50 | 3.50 | 1.50 | 0.2976 | 0.993 | 0.007 |
| FST-D | 6.75 | 3.00 | 1.50 | 0.2920 | 0.950 | 0.050 |
| FST-E | 7.00 | 3.00 | 1.50 | 0.2910 | 0.870 | 0.130 |

| Quadratic Non-Factorial Response Surface Methodology (RSM) Equation | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $Y_{FST}$ | Intercept | A | B | C | AB | AC | BC | $A^2$ | $B^2$ | $C^2$ |
| | 0.297 | 0.95 | 0.16 | 0.18 | 0.004 | 0.02 | 0.015 | 0.675 | 0.024 | 0.084 |
| Probability | p<0.01 | 0.01<= p <0.05 | | | 0.05<= p<0.10 | | | p>=0.10 | | |
| Lambda (λ) max | | 327nm | | Finest linearity Range | | | | 2.5-15µg/ml | | |
| Regression Equation | | y = 0.029x +0.005 | | | Recovery (%) | | | 100.92% | | |
| Repeatability (%RSD, n = 3) | | 0.998 | | | Limit of Detection/µg $ml^{-1}$ | | | 0.016 | | |
| Standard solution stability | | | | | | | | 0.995 | | |

**Table 3:** Checkpoint spaces prediction of finest variables levels of responses.

anticipated & desirability values (0.960 0to 0.995) via Lack of Fitness as error was found very lowest (varying between 0.007 and 0.15). Further, the solutions absorbance was measured against the blank at lambda max 327nm wavelength. Thus the low magnitudes of error as well as the significant values of response present investigation prove the high predictive ability of the response surface methodology. As well, this designed model of independent interactive can be used for "finer to finest" quantitative estimation best fitted method. Also, finest designed model has absorptive along with superior's in-terms of analytically sensitivity. The responses of model equation R-square (0.9998) found best as finest. Therefore, this model design space can be used to investigate its surface model or plot) which showed the independent effect of optimized significant finest levels of variables on response (Y) with-in limits and this higher recovery percentage indicated that there was no excipients interference. As well, indicated and concluded that Taguchi array via response surface "quadratic independent factorial" designed finest methodology can be further considered as finest for quantitative & quality reliable economically method of estimation.

## Conflict Of Interest

None to declare

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